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Metabolic score for insulin resistance as a predictor of mortality in heart failure with preserved ejection fraction: results from a multicenter cohort study

You Zhou[1], Yingli Xie[2], Laijing Du[2], Jingjing Dong[2] and Kunlun He[1,3*]

Abstract

Background The metabolic score for insulin resistance (METS-IR) has been validated as a novel, simple, and reliable surrogate marker for insulin resistance; however, its utility for evaluating the prognosis of heart failure with preserved ejection fraction (HFpEF) remains to be elucidated. Therefore, we aimed to analyze the association between METS-IR and the long-term prognosis of HFpEF.

Methods We enrolled a total of 4,702 participants with HFpEF in this study. The participants were divided into three groups according to METS-IR tertiles: (Ln [2 × fasting plasma glucose + fasting triglycerides] × body mass index) / (Ln [high-density lipoprotein cholesterol]). The occurrence of primary endpoints, including all-cause mortality and cardiovascular (CV) death, was documented.

Results There were 3,248 participants with HFpEF (mean age, 65.7 ± 13.8 years; male, 59.0%) in total who were included in the final analysis. The incidence of primary outcomes from the lowest to the highest METS-IR tertiles were 46.92, 86.01, and 124.04 per 1000 person-years for all-cause death and 26.75, 49.01, and 64.62 per 1000 person-years for CV death. The multivariate Cox hazards regression analysis revealed hazard ratios for all-cause and CV deaths of 2.48 (95% CI 2.10–2.93; $P < 0.001$) and 2.29 (95% CI 1.83–2.87; $P < 0.001$) when the highest and lowest METS-IR tertiles were compared, respectively. In addition, the predictive efficacy of METS-IR remained significant across various comorbidity subgroups (all $P < 0.05$). Further, adding the METS-IR to the baseline risk model for all-cause death improved the C-statistic value (0.690 for the baseline model vs. 0.729 for the baseline model + METS-IR, $P < 0.01$), the integrated discrimination improvement value (0.061, $P < 0.01$), the net reclassification improvement value (0.491, $P < 0.01$), and the clinical net benefit.

Conclusions An elevated METS-IR, which is associated with an increased mortality risk, is a potential valuable prognostic marker for individuals with HFpEF.

Keywords Heart failure with preserved ejection fraction, Metabolic score for insulin resistance, Insulin resistance, Mortality

*Correspondence:
Kunlun He
kunlunhe_301@163.com
[1]School of Medicine, Nankai University, No.94 Weijin Road, Nankai District, Tianjin 300071, China
[2]The First Affiliated Hospital and Clinical Medicine College, Henan University of Science and Technology, Luoyang 471003, China
[3]Medical Innovation Research Department of People's Liberation Army General Hospital, No.28 Fuxing Road, Haidian District, Beijing 100853, China

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Introduction

Heart failure (HF) is a major disease that affects the health and quality of life of approximately 64 million people worldwide [1]. Heart failure with preserved ejection fraction (HFpEF) is a distinct phenotype of HF, and it accounts for approximately 50% of all HF cases [2]. The proportion of individuals hospitalized due to HFpEF is rapidly increasing; these individuals have a poor prognosis, with a 5-year mortality rate of 53–74% [3]. Currently, therapeutic strategies that effectively improve adverse outcomes in HFpEF are extremely limited. Although existing clinical data support the ability of SGLT2 inhibitors to improve clinical outcomes in HFpEF [4], the underlying pathophysiological mechanisms of HFpEF remain poorly understood, and effective treatment options remain scarce [2]. Therefore, an in-depth exploration of prognostic factors and identification of populations with poor prognosis are of profound importance for enhancing risk management and improving disease outcomes.

HFpEF is frequently accompanied by multiple systemic abnormalities, and the burden of its comorbidities increases over time [2, 5]. Metabolic disturbance and inflammatory burden are common and significant comorbidities of HFpEF, and they are closely associated with its onset and progression [6]. Insulin resistance (IR), a central alteration in metabolic syndrome, is closely associated with various cardiovascular diseases (CVDs) [7]. Research has confirmed that IR also plays a significant role in the pathogenesis of HFpEF [8].

The current gold standard for assessing IR is the hyper insulinemic-euglycemic clamp (HEC); however, its clinical application is limited because of the time-consuming, expensive, and complicated nature of the procedure [9]. The metabolic score for insulin resistance (METS-IR) is easily calculated and reflects the interplay between glucose, lipid metabolism and body weight, which are the primary components of metabolic disorders [10, 11]. Further, METS-IR demonstrates a high degree of consistency with the HEC, and it can serve as an effective alternative marker for IR in clinical research [11]. Prior studies have found that METS-IR is associated with various CVDs and their risk factors, such as ischemic heart disease (IHD), diabetes, and hypertension [10–13].

There are currently limited data on the relationship between METS-IR and the prognosis of HFpEF. Despite the high prevalence of comorbidities in HFpEF, it remains unclear whether different comorbid conditions influence the prognostic relationship between METS-IR and HFpEF. Therefore, this study investigated the potential prognostic value of METS-IR in HFpEF and conducted further exploratory analyses in subjects with different comorbidities.

Methods

Study design and population

This was a retrospective, multicenter cohort study of participants with HFpEF who were hospitalized at The First Affiliated Hospital of Henan University of Science and Technology from January 1, 2016, to December 31, 2020, at the Second Affiliated Hospital from January 1, 2016, to December 31, 2019, and at the Sixth Medical Center of PLA General Hospital from January 1, 2016, to December 31, 2018. In reference to the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [14], the diagnosis of HFpEF required meeting the following three criteria: (1) symptoms and signs of HF; (2) LVEF ≥ 50%; and (3) left ventricular hypertrophy, left atrial enlargement, or diastolic dysfunction reported on echocardiography, accompanied by elevated NT-proBNP levels (>125 pg/ml for sinus rhythm or >365 pg/ml for atrial fibrillation). From the initial cohort of 4,702 participants, 1,454 were excluded according to the following criteria: (1) age < 18 years or pregnancy; (2) severe hepatic or renal dysfunction; (3) advanced cancer or connective tissue diseases; (4) lacking data on body mass index (BMI), fasting blood glucose (FBG), triglyceride (TG), or high-density lipoprotein cholesterol (HDL-C) at admission; and (5) in-hospital mortality or loss to follow-up. There were 3,248 subjects in total who were enrolled (1,916 men, 1,332 women; average age 65.7 ± 13.8 years). Further, subjects were categorized into three groups according to METS-IR tertiles, namely, T1 (METS-IR < 36.49, $n = 1083$), T2 (36.49 ≤ METS-IR < 43.96, $n = 1082$), and T3 (METS-IR ≥ 43.96, $n = 1083$) (Fig. 1). Finally, we evaluated the severity of comorbidities using the age-adjusted Charlson Comorbidity Index (ACCI) [15] and conducted subgroup stratifications based on these scores: ≤ 3 points, 4–6 points, and ≥ 7 points.

Ethics statement

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki, and it was approved by the ethics committees of the Affiliated Hospital of Henan University of Science and Technology (2023-03-K0026) and the PLA General Hospital (S2023-065-02). Owing to the retrospective design, the institutional review board waived the requirement for informed consent and ensured that all of the patient-related information was anonymized.

Data collection and definitions

Clinical data, including vital signs, laboratory tests, echocardiographic data, comorbidities, and medication details, were collected from an electronic medical records system. The METS-IR was calculated as Ln [2 × FBG (mg/dL) + fasting TG (mg/dL)] × BMI (kg/m^2) / Ln [HDL-C (mg/dL)] [10]. The mean arterial pressure

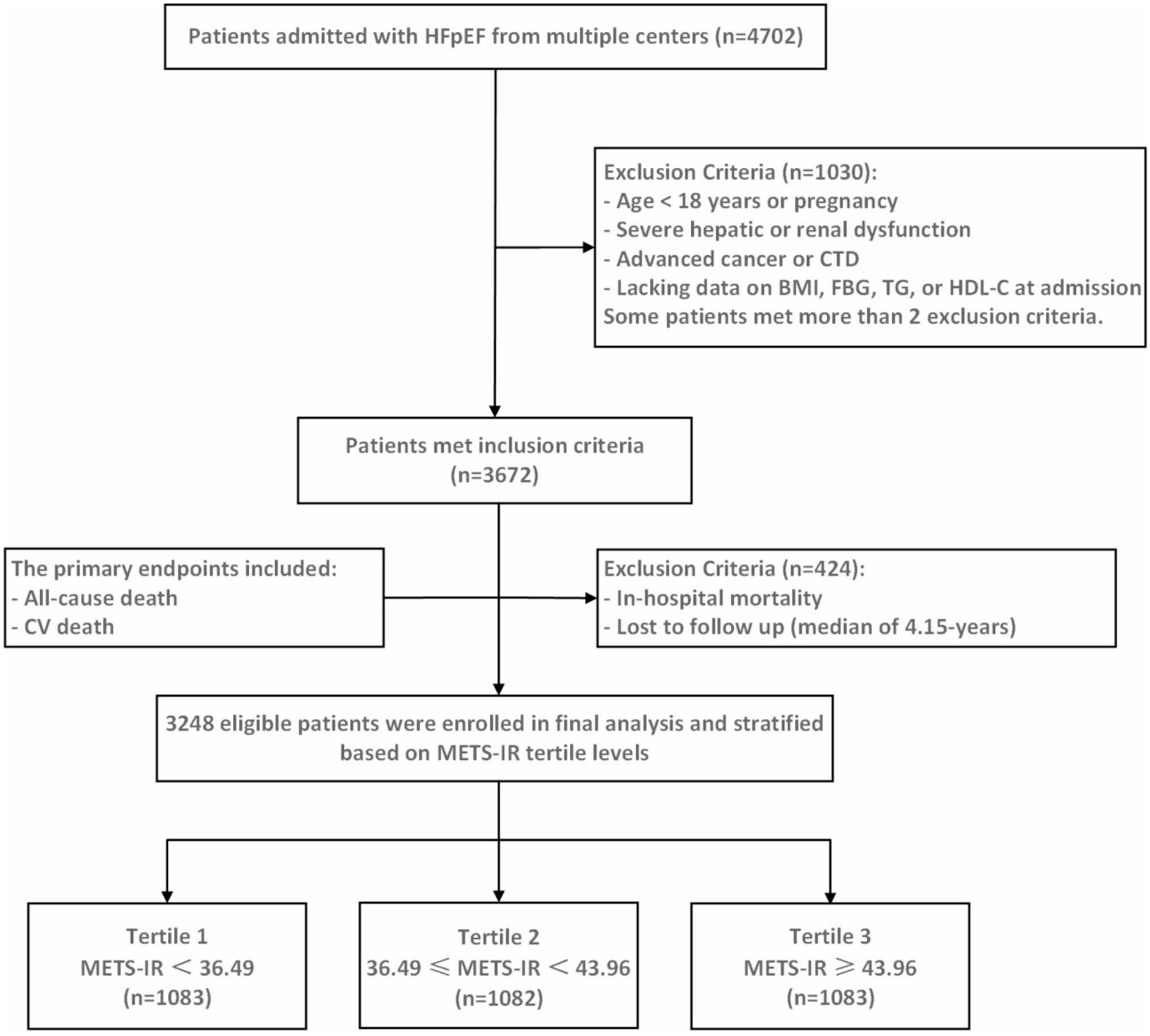
Patients admitted with HFpEF from multiple centers (n=4702)
Exclusion Criteria (n=1030):
- Age < 18 years or pregnancy
- Severe hepatic or renal dysfunction
- Advanced cancer or CTD
- Lacking data on BMI, FBG, TG, or HDL-C at admission
Some patients met more than 2 exclusion criteria.
Patients met inclusion criteria (n=3672)
The primary endpoints included:
- All-cause death
- CV death
Exclusion Criteria (n=424):
- In-hospital mortality
- Lost to follow up (median of 4.15-years)
3248 eligible patients were enrolled in final analysis and stratified based on METS-IR tertile levels
Tertile 1
METS-IR < 36.49
(n=1083)
Tertile 2
36.49 ⩽ METS-IR < 43.96
(n=1082)
Tertile 3
METS-IR ⩾ 43.96
(n=1083)

Fig. 1 Flow diagram of participants selection. *HFpEF* heart failure with preserved ejection fraction, *CTD* connective tissue diseases, *BMI* body mass Index, *FBG* fasting blood glucose, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *CV death* cardiovascular death, *METS-IR* the metabolic score for insulin resistance

(MAP) was calculated using the following formula: (systolic blood pressure + 2 × diastolic blood pressure)/3. BMI was determined using the following formula: body weight (kg) / [height (m)]^2, expressed as kg/m^2. Chronic kidney disease was determined through medical history or identified by an estimated glomerular filtration rate below 60 mL/min per 1.73 m^2, according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16]. A clinical diagnosis of diabetes was further confirmed through the following criteria: a prior diagnosis of diabetes and/or FBG ≥ 7.0 mmol/L and/or random blood glucose ≥ 11.1 mmol/L and/or the use of hypoglycemic agents. Hypoglycemic medications included those prescribed at discharge as well as oral hypoglycemic drugs used during hospitalization (excluding SGLT2 inhibitors, as these were not exclusively used for participants with diabetes).

Follow-up and outcomes

Prognostic data were acquired through telephone follow-ups or by examining relevant electronic medical records over a median follow-up period of 4.2 years (interquartile range (IQR), 3.0–5.1 years). The primary outcomes were all-cause mortality and cardiovascular (CV) death.

Statistical analysis

The characteristics of the participants were delineated according to the tertiles of METS-IR. Continuous

variables are reported as the mean ± standard deviation or median with IQR, depending on the normality of their distribution. For continuous data, comparisons were made using one-way ANOVA for normally distributed data or the Kruskal–Wallis test for non-normally distributed data. Categorical variables are presented as frequencies and percentages, with group differences evaluated using the chi-squared test or Fisher's exact test, as appropriate.

The cumulative incidence of the primary endpoints was estimated using the Kaplan–Meier method, and group differences were evaluated using the log-rank test. The association between METS-IR and the incidence of primary outcomes was investigated using Cox proportional hazards models. Predictors that were significant in univariate Cox analyses (Table S1) or deemed clinically important were included as covariates in the multivariate Cox model. Furthermore, the multivariate analysis accounted for collinearity among the variables. METS-IR was analyzed as both a categorical variable (with the lowest tertile as the reference) and a continuous variable (per standard deviation (SD) increase). The linear trends across METS-IR tertiles were evaluated using the within-tertile median as a continuous variable. Two additional models were fitted (in addition to the unadjusted model): Model 1 controlled for age, gender, heart rate, New York Heart Association classification and left ventricular ejection fraction (LVEF), and Model 2 included all of the variables from Model 1 with additional adjustments for NT-proBNP, hemoglobin, creatinine, low-density lipoprotein cholesterol (LDL), atrial fibrillation, hypertension, stroke, peripheral arterial disease, ischemic etiology, statins, ACEI/ARB/ARNI, beta-blocker, calcium channel blockers, mineralocorticoid antagonists, diuretics, insulin, and SGLT2 inhibitors. Multiple imputations using chained equations were employed to handle missing covariates. The proportional hazards assumption was assessed utilizing Schoenfeld residuals, which revealed no potential violations. Propensity score matching (PSM) was used to adjust for covariates, thus guaranteeing comparability among groups when analyzing baseline characteristics. In addition, restricted cubic spline (RCS) regression model with three assumed knots was conducted to delineate the relationship between METS-IR and the hazard ratio (HR) [17], adjusted for the variables in Model 2. We carried out exploratory analyses across various subgroups, categorized by different comorbidities and their severity as indicated by ACCI scores. We used the likelihood ratio test to evaluate interactions between these subgroups.

Finally, the incremental effect of METS-IR on risk stratification was further evaluated using the C-statistic, net reclassification index (NRI), and integrated discrimination improvement (IDI), with the baseline model (MAGGIC score + NT-proBNP) serving as the reference. NRI measures the extent of improvement in correctly reclassifying individuals into appropriate risk categories, while IDI quantifies the overall enhancement in the model's discrimination ability across all risk levels. Additionally, we performed exploratory analyses to evaluate the incremental effect of METS-IR among different sex subgroups (male and female) and age subgroups (under 65 years and 65 years or older). Statistical analyses were performed using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P value < 0.05 was considered to be significant.

Results

Participant characteristics

A total of 3,248 eligible participants were included in the analysis, with a mean age of 65.7 years; 59.0% were male. Table 1 details the baseline population characteristics, categorized by METS-IR tertiles. Participants with higher baseline METS-IR were older and had a greater prevalence of comorbidities, including hypertension, diabetes, chronic kidney disease, stroke, and ischemic etiology. This group also had a higher incidence of using antiplatelet agents, ACEI/ARB/ARNI, beta-blockers, calcium channel blockers, statins, diuretics, SGLT2 inhibitors, and other hypoglycemic drugs, but a lower incidence of digoxin use. In addition, this group exhibited higher BMI, MAP, white blood cell count, platelet count, creatinine, FBG, TG, total cholesterol, LDL, and NT-proBNP levels, but lower eGFR, HDL-C, and LVEF (all P < 0.05).

Correlations between METS-IR and adverse outcomes

Over a median follow-up of 4.15 years, the incidence of primary events was 83.08 per 1000 person-years for all-cause death and 45.52 per 1000 person-years for CV death. The incidence of primary events from the lowest to the highest METS-IR tertiles were 46.92, 86.01, and 124.04 per 1000 person-years for all-cause death and 26.75, 49.01, and 64.62 per 1000 person-years for CV death. The cumulative incidence of both all-cause death and CV death increased with higher METS-IR tertiles (Fig. 2, log-rank test, both P < 0.001). The RCS regression model also revealed that higher levels of METS-IR was associated with an increased risk of all-cause death (Model 2: HR per SD increase = 1.26, 95% CI 1.21–1.33) and CV death (Model 2: HR per SD increase = 1.23, 95% CI 1.16–1.32) (both P < 0.001) (Fig. S1).

Table 2 displays the three Cox regression models utilized to evaluate the associations between METS-IR and outcomes. In all three of the models, the highest METS-IR tertile was linked to a higher incidence of all-cause mortality (unadjusted Model: HR 2.61, 95% CI 2.23–3.06, P < 0.001; Model 1: HR 2.46, 95% CI 2.09–2.89, P < 0.001; Model 2: HR 2.48, 95% CI 2.10–2.93, P < 0.001).

Table 1 Baseline characteristics of the study population based on tertiles of METS-IR

Variables	Tertile of METS-IR			*P* value
	T1 (*n* = 1083)	T2 (*n* = 1082)	T3 (*n* = 1083)	
METS-IR	< 36.49	36.49–43.96	≥ 43.96	**< 0.001**
Demographics				
Age (years)	65.0 (54.0–76.0)	66.0 (56.0–76.0)	67.0 (58.0–77.0)	**< 0.001**
Male (%)	613 (56.60%)	651 (60.17%)	652 (60.20%)	0.147
Medical measurements				
BMI (kg/m^2)	21.8 (19.9–23.4)	25.5 (24.2–27.1)	29.4 (27.2–32.1)	**< 0.001**
MAP (mmHg)	93.3 (84.0-102.7)	94.3 (85.3-103.3)	98.3 (89.0-107.8)	**< 0.001**
HR (bpm)	77.0 (68.0–88.0)	76.0 (68.0–88.0)	76.0 (67.0–86.0)	0.490
NYHA classification (%)				0.773
I-II	604 (55.77%)	602 (55.64%)	586 (54.11%)	
III	375 (34.63%)	375 (34.66%)	377 (34.81%)	
IV	104 (9.60%)	105 (9.70%)	120 (11.08%)	
Medical history (%)				
AF	419 (38.69%)	396 (36.60%)	382 (35.27%)	0.251
CKD	329 (30.38%)	364 (33.64%)	422 (38.97%)	**< 0.001**
Hypertension	621 (57.34%)	741 (68.48%)	781 (72.11%)	**< 0.001**
Diabetes	365 (33.70%)	468 (43.25%)	576 (53.19%)	**< 0.001**
Stroke	221 (20.41%)	251 (23.20%)	278 (25.67%)	**0.015**
PAD	115 (10.62%)	133 (12.29%)	150 (13.85%)	0.072
Ischemic etiology	387 (35.73%)	447 (41.31%)	537 (49.58%)	**< 0.001**
Laboratory measurements				
WBC (10^9/L)	6.02 (4.95–7.68)	6.41 (5.13–7.86)	6.66 (5.48–8.32)	**< 0.001**
Hemoglobin (g/L)	128.0 (114.0-142.0)	129.2 (117.0-143.0)	130.0 (114.0-143.1)	0.276
Platelets (10^9/L)	191.0 (150.0-234.0)	202.0 (162.0-247.0)	207.0 (164.0-253.0)	**< 0.001**
ALT (U/L)	21.0 (15.0–32.0)	20.9 (14.0–32.0)	22.0 (14.6–35.0)	0.229
AST (U/L)	21.9 (17.0–30.0)	21.4 (17.1–30.0)	22.0 (16.9–33.0)	0.735
Creatinine (umol/L)	75.0 (62.0-91.3)	76.3 (65.0–93.0)	78.9 (65.4–101.0)	**< 0.001**
eGFR (ml/min/1.73m^2)	84.3 (63.9–99.1)	82.2 (63.3–95.7)	80.2 (58.5–94.7)	**< 0.001**
FBG (mmol/L)	5.12 (4.57–5.99)	5.63 (4.86–6.85)	6.24 (5.18-8.00)	**< 0.001**
TG (mmol/L)	1.00 (0.74–1.42)	1.24 (0.89–1.77)	1.56 (1.12–2.16)	**< 0.001**
TC (mmol/L)	3.77 (3.10–4.60)	3.90 (3.21–4.68)	4.07 (3.42–4.84)	**< 0.001**
LDL-C (mmol/L)	2.13 (1.62–2.82)	2.26 (1.73–2.87)	2.39 (1.89-3.00)	**< 0.001**
HDL-C (mmol/L)	1.24 (1.05–1.48)	1.07 (0.90–1.26)	0.88 (0.73–1.07)	**< 0.001**
Potassium (mmol/L)	3.97 (3.68–4.31)	3.94 (3.66–4.28)	3.96 (3.66–4.27)	0.248
NT-proBNP (pg/ml)	1226.0 (609.5–3510.0)	1242.5 (802.1–3225.0)	1302.0 (852.5-3381.5)	**< 0.001**
Echocardiography				
LVEF (%)	60.0 (55.0–65.0)	59.0 (54.0–64.0)	58.0 (53.0–64.0)	**< 0.001**
Medications at discharge (%)				
Antiplatelet agents	531 (49.03%)	605 (55.91%)	672 (62.05%)	**< 0.001**
ACEI/ARB/ARNI	350 (32.32%)	425 (39.28%)	487 (44.97%)	**< 0.001**
Beta-blocker	687 (63.43%)	731 (67.56%)	800 (73.87%)	**< 0.001**
CCB	240 (22.16%)	284 (26.25%)	319 (29.46%)	**< 0.001**
Statins	563 (51.99%)	680 (62.85%)	740 (68.33%)	**< 0.001**
Digoxin	239 (22.07%)	192 (17.74%)	161 (14.87%)	**< 0.001**
Mineralocorticoid antagonists	695 (64.17%)	696 (64.33%)	669 (61.77%)	0.384
Diuretics	594 (54.85%)	607 (56.10%)	670 (61.87%)	**0.002**
SGLT2 inhibitors	43 (3.97%)	75 (6.93%)	103 (9.51%)	**<0.001**
Insulin	52 (4.80%)	114 (10.54%)	142 (13.11%)	**< 0.001**
Other oral antidiabetic agents	235 (21.70%)	274 (25.32%)	349 (32.23%)	**< 0.001**
All-cause death				
Incidence/1000 person-years	46.92	86.01	124.04	**< 0.001**

Table 1 (continued)

Variables	Tertile of METS-IR			*P* value
	T1 (*n* = 1083)	T2 (*n* = 1082)	T3 (*n* = 1083)	
CV death				
Incidence/1000 person-years	26.75	49.01	64.62	**< 0.001**

METS-IR the metabolic score for insulin resistance, *BMI* body mass index, *MAP* mean arterial pressure, *HR* heart rate, *NYHA* New York Heart Association, *AF* atrial fibrillation, *CKD* chronic kidney disease, *PAD* peripheral arterial disease, *WBC* white blood cell, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *ACEI/ARB/ARNI* angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitors, *CCB* calcium channel blockers, *SGLT2 inhibitors* sodium-glucose co-transporter-2 inhibitors, *CV death* cardiovascular death. *P* values < 0.05 are presented in bold

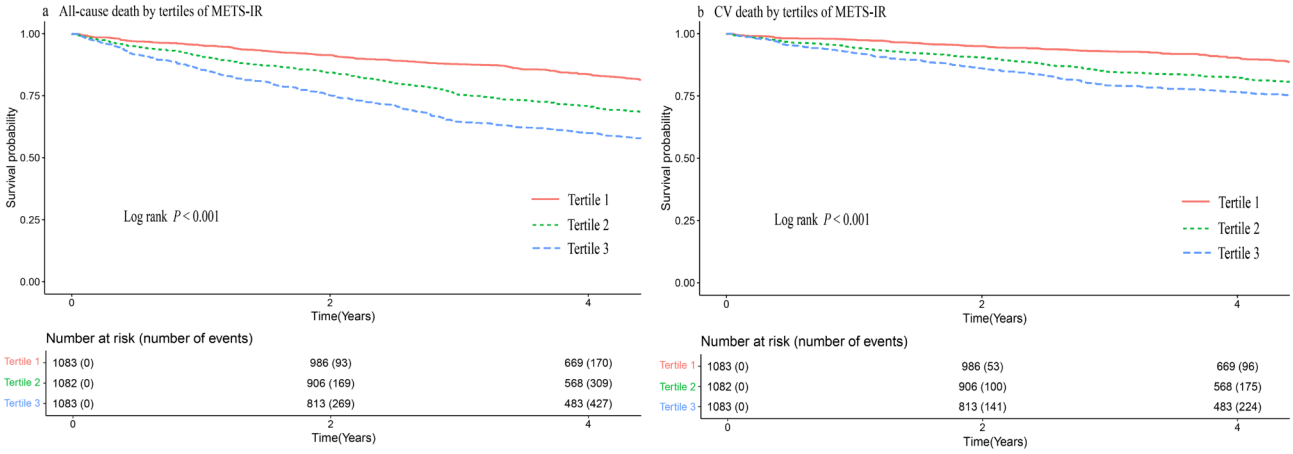
a All-cause death by tertiles of METS-IR
Survival probability
Log rank P < 0.001
Tertile 1
Tertile 2
Tertile 3
Time(Years)
Number at risk (number of events)
Tertile 1 1083 (0) 986 (93) 669 (170)
Tertile 2 1082 (0) 906 (169) 568 (309)
Tertile 3 1083 (0) 813 (269) 483 (427)
b CV death by tertiles of METS-IR
Survival probability
Log rank P < 0.001
Tertile 1
Tertile 2
Tertile 3
Time(Years)
Number at risk (number of events)
Tertile 1 1083 (0) 986 (53) 669 (96)
Tertile 2 1082 (0) 906 (100) 568 (175)
Tertile 3 1083 (0) 813 (141) 483 (224)

Fig. 2 Kaplan-Meier estimation of (**a**) all-cause death and (**b**) CV death by tertiles of METS-IR in HFpEF. *CV death* cardiovascular death, *METS-IR* the metabolic score for insulin resistance, *HFpEF* heart failure with preserved ejection fraction

As a continuous variable, METS-IR was also significantly associated with all-cause death (Model 2: HR 1. 26, 95% CI 1.21–1.33, $P<0.001$). Similar results were observed in the multivariate Cox proportional hazards analysis for METS-IR and CV death (Model 2: HR 2.29, 95% CI 1.83–2.87, $P<0.001$ for the categorical variable with T1 vs. T3; and HR 1.23, 95% CI 1.16–1.32, $P<0.001$ for the continuous variable).

In addition, to assess the consistency of our findings, PSM was conducted to adjust for key confounding variables such as age, sex, comorbidities, and treatments across the three groups (Table S2). The results remained unchanged even after the PSM analysis: the highest METS-IR tertile was also linked to higher incidences of all-cause mortality (Model 2: HR 2.27, 95% CI 1.86–2.77, $P<0.001$) and CV death (Model 2: HR 2.13, 95% CI 1.63–2.77, $P<0.001$) (Table S3).

Implications of METS-IR on survival outcomes in subgroups categorized by comorbidities

Further exploratory analyses were conducted across subgroups categorized by different comorbidities and ACCI scores. The Kaplan–Meier analysis revealed significant differences in the risk of primary endpoints among the three METS-IR tertiles across different comorbidity subgroups, including hypertension, diabetes, ischemic etiology, atrial fibrillation, CKD, obesity, stroke, and dyslipidemia (all log-rank test, $P<0.001$) (Figs. S2, S3).

The results of the multivariate Cox proportional hazards models for the relationship between the METS-IR and all-cause death among different comorbidities are displayed in Fig. 3. The association between METS-IR and all-cause mortality remained consistently strong across comorbidities, even after adjusting for multiple factors, thus indicating its persistent link to poor prognosis in all of the subgroups (all $P<0.05$). The relationship between METS-IR and CV death exhibited similar outcomes across all of the groups (Table S4).

We conducted further exploratory analyses to investigate the prognostic value of METS-IR across different ACCI scores, which reflected the severity of comorbidities. After excluding individuals with missing data necessary for ACCI scoring, a total of 2,622 subjects (from the original population of $n=3,248$) were ultimately included in the ACCI scores analysis. Participants were divided into three groups based upon ACCI scores, namely, ≤ 3 points, 4–6 points, and ≥7 points. The previously discovered associations between METS-IR and adverse outcomes remained unchanged in the ACCI analysis population, as well as across the three designated subgroups (all $P<0.05$). In addition, we found that although the interaction of the prognostic efficacy of METS-IR

Table 2 HRs (95% CI) of primary outcomes according to METS-IR tertiles

Categories	Incidence/ 1000 person-y	Unadjusted			Model 1			Model 2		
		HR (95% CI)	*P*-value	*P* for trend	HR (95% CI)	*P*-value	*P* for trend	HR (95% CI)	*P*-value	*P* for trend
All-cause death										
Continuous variable per SD		1.32 (1.25–1.38)	**< 0.001**		1.28 (1.22–1.34)	**< 0.001**		1.26 (1.21–1.33)	**< 0.001**	
Tertile[a]				**< 0.001**			**< 0.001**			**< 0.001**
T1 ($n = 1083$)	46.92	Ref.			Ref.			Ref.		
T2 ($n = 1082$)	86.01	1.82 (1.54–2.15)	**< 0.001**		1.76 (1.49–2.08)	**< 0.001**		1.78 (1.50–2.11)	**< 0.001**	
T3 ($n = 1083$)	124.04	2.61 (2.23–3.06)	**< 0.001**		2.46 (2.09–2.89)	**< 0.001**		2.48 (2.10–2.93)	**< 0.001**	
CV death										
Continuous variable per SD		1.28 (1.20–1.37)	**< 0.001**		1.24 (1.16–1.33)	**< 0.001**		1.23 (1.16–1.32)	**< 0.001**	
Tertile[a]				**< 0.001**			**< 0.001**			**< 0.001**
T1 ($n = 1083$)	26.75	Ref.			Ref.			Ref.		
T2 ($n = 1082$)	49.01	1.81 (1.46–2.27)	**< 0.001**		1.75 (1.40–2.18)	**< 0.001**		1.77 (1.42–2.22)	**< 0.001**	
T3 ($n = 1083$)	64.62	2.38 (1.92–2.95)	**< 0.001**		2.23 (1.79–2.76)	**< 0.001**		2.29 (1.83–2.87)	**< 0.001**	

HR hazard ratio, *CI* confidence interval, *METS-IR* the metabolic score for insulin resistance, *SD* standard deviation, *CV death* cardiovascular death

Model 1: adjusted for age, gender, heart rate, NYHA classification and LVEF

Model 2: adjusted for Model 1 + NT-proBNP, hemoglobin, creatinine, LDL, AF, hypertension, stroke, PAD, ischemic etiology, statins, ACEI/ARB/ARNI, beta-blocker, CCB, mineralocorticoid antagonists, diuretics, insulin, and SGLT2 inhibitors

[a]METS-IR: T1 (< 36.49), T2 (36.49–43.96), T3 (≥ 43.96). *P* values < 0.05 are presented in bold

across the three subgroups did not reach statistical significance ($P > 0.05$), the trend suggested seemingly opposite patterns for all-cause mortality and CV death. Specifically, the predictive efficacy of METS-IR for all-cause mortality, based on Model 2, was more pronounced in the group with the highest ACCI scores: HR 2.71, 95% CI 2.04–3.61, for the ≥7 scores group, comparing the lowest (T1) to the highest tertile (T3). However, this trend was not observed for CV death. Instead, the predictive efficacy of METS-IR for CV death appeared to be stronger in the subgroup with the lowest ACCI scores (Table S5).

Incremental impact of METS-IR on risk stratification in HFpEF

Finally, we assessed the incremental value of METS-IR for enhancing the baseline risk model, including NT-proBNP and the MAGGIC score [18] (Fig. 4; Table 3). The cut-off value for METS-IR in predicting mortality was calculated to be 40.50, with a sensitivity of 63.30% and a specificity of 57.34%. The addition of METS-IR significantly improved risk prediction beyond the baseline risk model, with the C-statistic increasing from 0.690 to 0.729 for 3-year mortality ($P < 0.01$). Analysis of NRI and IDI demonstrated statistically significant enhancements in predictive value: continuous NRI (95% CI: 0.491 [0.412–0.569], $P < 0.01$) and IDI (95% CI: 0.061 [0.052–0.070], $P < 0.01$). The incremental impact of METS-IR persisted even across different subgroups stratified by sex and age (Table 3). Decision curve analysis revealed the net benefit of the new model (baseline risk model + METS-IR) was superior to the baseline risk model alone (Fig. S4).

Discussion

To our knowledge, this study represents the first investigation into the association between METS-IR and the long-term outcomes in subjects with HFpEF. The principal findings of our study were as follows: (1) METS-IR was closely associated with adverse outcomes, and this association remained consistent across various comorbidities; (2) the predictive power of METS-IR for all-cause death and CV death appeared to follow different trends for individuals with higher or lower ACCI scores; and (3) adding METS-IR to the baseline risk model significantly enhanced the predictive efficacy and clinical net benefit. In summary, our research substantiated the potential use of METS-IR as an independent and valuable prognostic marker for the prognosis of HFpEF.

HFpEF is a common, complex, and heterogeneous syndrome. With advances in modern medical technology and enhanced understanding of health management, the incidence of HF, particularly heart failure with reduced ejection fraction (HFrEF), is decreasing; the incidence of HFpEF, however, is gradually increasing [19]. A survey of national hospitalizations in the United States revealed

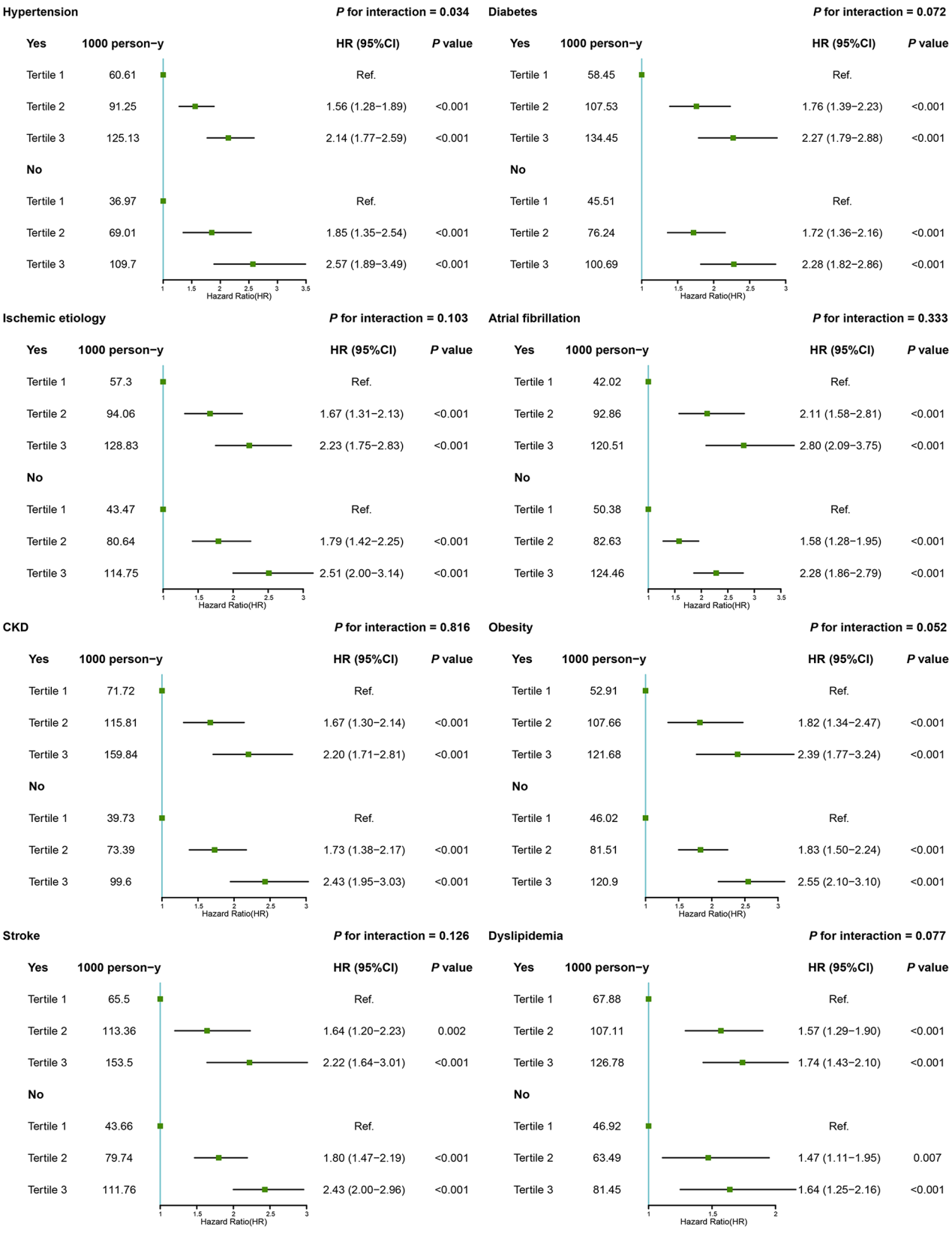
Hypertension
P for interaction = 0.034
Yes 1000 person−y HR (95%CI) P value
Tertile 1 60.61 Ref.
Tertile 2 91.25 1.56 (1.28−1.89) <0.001
Tertile 3 125.13 2.14 (1.77−2.59) <0.001
No
Tertile 1 36.97 Ref.
Tertile 2 69.01 1.85 (1.35−2.54) <0.001
Tertile 3 109.7 2.57 (1.89−3.49) <0.001
Hazard Ratio(HR)
Diabetes
P for interaction = 0.072
Yes 1000 person−y HR (95%CI) P value
Tertile 1 58.45 Ref.
Tertile 2 107.53 1.76 (1.39−2.23) <0.001
Tertile 3 134.45 2.27 (1.79−2.88) <0.001
No
Tertile 1 45.51 Ref.
Tertile 2 76.24 1.72 (1.36−2.16) <0.001
Tertile 3 100.69 2.28 (1.82−2.86) <0.001
Hazard Ratio(HR)
Ischemic etiology
P for interaction = 0.103
Yes 1000 person−y HR (95%CI) P value
Tertile 1 57.3 Ref.
Tertile 2 94.06 1.67 (1.31−2.13) <0.001
Tertile 3 128.83 2.23 (1.75−2.83) <0.001
No
Tertile 1 43.47 Ref.
Tertile 2 80.64 1.79 (1.42−2.25) <0.001
Tertile 3 114.75 2.51 (2.00−3.14) <0.001
Hazard Ratio(HR)
Atrial fibrillation
P for interaction = 0.333
Yes 1000 person−y HR (95%CI) P value
Tertile 1 42.02 Ref.
Tertile 2 92.86 2.11 (1.58−2.81) <0.001
Tertile 3 120.51 2.80 (2.09−3.75) <0.001
No
Tertile 1 50.38 Ref.
Tertile 2 82.63 1.58 (1.28−1.95) <0.001
Tertile 3 124.46 2.28 (1.86−2.79) <0.001
Hazard Ratio(HR)
CKD
P for interaction = 0.816
Yes 1000 person−y HR (95%CI) P value
Tertile 1 71.72 Ref.
Tertile 2 115.81 1.67 (1.30−2.14) <0.001
Tertile 3 159.84 2.20 (1.71−2.81) <0.001
No
Tertile 1 39.73 Ref.
Tertile 2 73.39 1.73 (1.38−2.17) <0.001
Tertile 3 99.6 2.43 (1.95−3.03) <0.001
Hazard Ratio(HR)
Obesity
P for interaction = 0.052
Yes 1000 person−y HR (95%CI) P value
Tertile 1 52.91 Ref.
Tertile 2 107.66 1.82 (1.34−2.47) <0.001
Tertile 3 121.68 2.39 (1.77−3.24) <0.001
No
Tertile 1 46.02 Ref.
Tertile 2 81.51 1.83 (1.50−2.24) <0.001
Tertile 3 120.9 2.55 (2.10−3.10) <0.001
Hazard Ratio(HR)
Stroke
P for interaction = 0.126
Yes 1000 person−y HR (95%CI) P value
Tertile 1 65.5 Ref.
Tertile 2 113.36 1.64 (1.20−2.23) 0.002
Tertile 3 153.5 2.22 (1.64−3.01) <0.001
No
Tertile 1 43.66 Ref.
Tertile 2 79.74 1.80 (1.47−2.19) <0.001
Tertile 3 111.76 2.43 (2.00−2.96) <0.001
Hazard Ratio(HR)
Dyslipidemia
P for interaction = 0.077
Yes 1000 person−y HR (95%CI) P value
Tertile 1 67.88 Ref.
Tertile 2 107.11 1.57 (1.29−1.90) <0.001
Tertile 3 126.78 1.74 (1.43−2.10) <0.001
No
Tertile 1 46.92 Ref.
Tertile 2 63.49 1.47 (1.11−1.95) 0.007
Tertile 3 81.45 1.64 (1.25−2.16) <0.001
Hazard Ratio(HR)

Fig. 3 Forest plot of all-cause death according to tertiles of METS-IR in HFpEF across different subgroups adjusted for Model 2. *HR* hazard ratio, *CI* confidence interval, *METS-IR* the metabolic score for insulin resistance, *HFpEF* heart failure with preserved ejection fraction, *CKD* chronic kidney disease

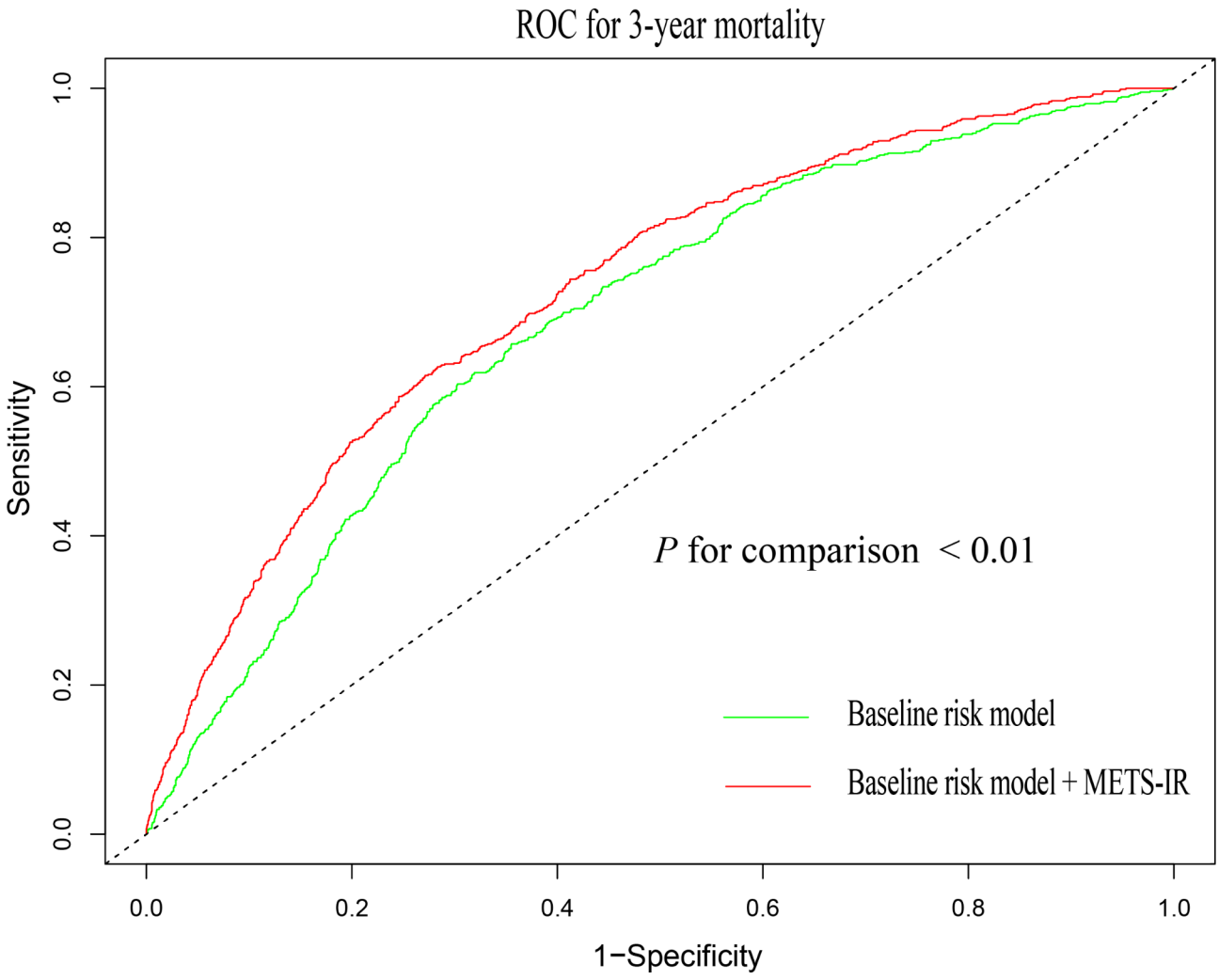

Fig. 4 ROC curves evaluating the incremental effect of METS-IR beyond the baseline risk model in HFpEF. *ROC curve* receiver operator characteristic curve, *METS-IR* the metabolic score for insulin resistance, *HFpEF* heart failure with preserved ejection fraction, *MAGGIC score* Meta-analysis Global Group in Chronic Heart Failure score. The baseline risk model includes the MAGGIC score and NT-proBNP

that the number of HFpEF hospitalizations more than doubled over a decade, increasing from 189,260 in 2008 to 495,095 in 2018 [20, 21]. Although the high prevalence and extensive impact of HFpEF are well recognized, the lack of effective treatment options has resulted in poor survival rates. In the Get With The Guidelines—HF registry, linked with Medicare data for longitudinal follow-up, the 5-year mortality rate was 75.7% for those with HFpEF and 75.3% for those with HFrEF [22]. Studies on the pathogenesis of HFpEF are still in an exploratory stage, and the underlying mechanisms of this condition have not been fully elucidated. Studies currently suggest that HFpEF is associated not only with hypertension but also with obesity, diabetes, dysregulated lipid metabolism, and other conditions [23–25].

The modern prevalence of metabolic syndrome is closely linked to contemporary lifestyles marked by high-calorie diets, sedentariness, and reduced physical activity [26].

Insulin resistance (IR) is a central feature of this syndrome, clinically characterized by a decrease in the biological efficacy of insulin and a reduced ability of tissues to absorb glucose. Research has confirmed that hyperglycemia induced by IR can lead to CVDs through multiple pathways, including dyslipidemia, atherosclerosis, energy metabolism disorders, and endothelial dysfunction [27, 28]. Furthermore, IR may precipitate or intensify the progression of HF, especially HFpEF [8]. One cohort study of 22,681 participants from four communities utilized the Homeostatic Model Assessment of Insulin Resistance to evaluate levels of IR. The incidence rates of HFrEF and HFpEF were analyzed over a median follow-up duration of 12 years. They found that IR was associated with HFpEF (HR: 1.20 per 1-SD increase; 95% CI: 1.05–1.37), but not with HFrEF (HR: 0.99; 95% CI: 0.88–1.11), with

Table 3 Evaluation the incremental effect of adding METS-IR to the baseline risk model to predict 3-year mortality

Groups	C-Statistic (95% CI)	*P* value	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value
Overall (*n* = 3248)						
Baseline risk model[a]	0.690 (0.668–0.709)	Ref.	-	Ref.	-	Ref.
Baseline risk model + METS-IR	0.729 (0.709–0.749)	**< 0.01**	0.491 (0.412–0.569)	**< 0.01**	0.061 (0.052–0.070)	**< 0.01**
Male (*n* = 1916)						
Baseline risk model	0.671 (0.644–0.699)	Ref.	-	Ref.	-	Ref.
Baseline risk model + METS-IR	0.713 (0.686–0.740)	**< 0.01**	0.427 (0.324–0.530)	**< 0.01**	0.053 (0.042–0.064)	**< 0.01**
Female (*n* = 1332)						
Baseline risk model	0.706 (0.675–0.737)	Ref.	-	Ref.	-	Ref.
Baseline risk model + METS-IR	0.751 (0.721–0.781)	**< 0.01**	0.558 (0.437–0.679)	**< 0.01**	0.072 (0.057–0.088)	**< 0.01**
Age < 65 years (*n* = 1479)						
Baseline risk model	0.641 (0.601–0.680)	Ref.	-	Ref.	-	Ref.
Baseline risk model + METS-IR	0.709 (0.673–0.745)	**< 0.01**	0.505 (0.365–0.646)	**< 0.01**	0.044 (0.032–0.057)	**< 0.01**
Age ≥ 65 years (*n* = 1769)						
Baseline risk model	0.633 (0.606–0.660)	Ref.	-	Ref.	-	Ref.
Baseline risk model + METS-IR	0.696 (0.670–0.723)	**< 0.01**	0.476 (0.379–0.574)	**< 0.01**	0.071 (0.059–0.084)	**< 0.01**

METS-IR the metabolic score for insulin resistance, *NRI* net reclassification improvement, *IDI* integrated discrimination improvement, *CI* confidence interval, *MAGGIC score* Meta-analysis Global Group in Chronic Heart Failure score. *P* values < 0.05 are presented in bold

[a]The baseline risk model includes the MAGGIC score and NT-proBNP

a statistically significant difference in the comparison between HFpEF and HFrEF ($P<0.05$) [29]. This further substantiated the close association between IR and HFpEF. Importantly, a vicious cycle can form between IR and HR; IR is a significant risk factor for the onset and progression of HF, while HF can in turn exacerbate the degree of IR [7, 30].

METS-IR is a novel non-insulin-dependent score used to assess the degree of IR that shows high concordance with HEC, the gold standard for measuring IR [11]. A large ($n=116,855$) cohort study from China assessed the relationship between METS-IR and the incidence of diabetes by stratifying participants into quartiles based on their METS-IR scores. The results revealed a significant association between METS-IR and the development of diabetes after multivariable adjustment (HR: 1.08; 95% CI: 1.07–1.08, $P<0.05$). Further, individuals in Quartile 4 had a 6.26-fold higher risk of developing diabetes than those in Quartile 1 [31]. In a study involving 17,943 non-diabetic Korean participants, 332 developed IHD over the follow-up period; the study observed an increase in the incidence of IHD corresponding to higher METS-IR. The HRs of IHD for METS-IR quartiles 1–4 were as follows (after adjusting for potential confounders): 1.00, 1.62 (95% CI 1.04–2.53), 1.87 (95% CI 1.20–2.91), and 2.11 (95% CI 1.35–3.30), thus indicating a clear trend of increased risk with elevated METS-IR levels [12]. Several studies have demonstrated an association between METS-IR and adverse outcomes, particularly mortality. For instance, data from a prospective cohort study in China involving 14,234 individuals with hypertension revealed that, after adjusting for multiple factors, METS-IR was significantly and positively associated with both all-cause mortality and CV death (both P for trend <0.05) [32]. Similarly, another study explored the relationship between METS-IR and adverse cardiovascular events, including cardiac death, in individuals with ischemic cardiomyopathy and type 2 diabetes mellitus. Multivariate Cox proportional hazards regression showed that the HR for the highest versus the lowest METS-IR tertiles was 1.89 (95% CI: 1.61–2.20), indicating an increased incidence of adverse events with higher METS-IR tertiles [33]. Moreover, METS-IR has also been found to be a reliable prognostic predictor for adverse outcomes, including all-cause mortality, in individuals with premature coronary artery disease [34].

However, current research on the relationship between METS-IR and the prognosis of HFpEF is very limited. Our study found a positive correlation between METS-IR and the incidence of adverse outcomes in HFpEF (HR: 1.26 per 1-SD increase; 95% CI: 1.21–1.33 for all-cause death and HR: 1.23 per 1-SD increase; 95% CI: 1.16–1.32 for CV death), and this association persisted across various comorbidities (all $P<0.05$). We hypothesize that the primary mechanisms underlying this relationship are the various adverse effects of IR on HF: First, the state of IR alters the metabolic environment through various complex signaling pathways, leading to maladaptive responses in the myocardium and inducing myocardial damage. These adverse effects include impaired mitochondrial oxidative capacity and dysfunction, oxidative stress, inflammation, and myocardial fibrosis [35]; Second, hyperinsulinemia, a hallmark of IR, activates and enhances sympathetic nervous system activity, resulting in cardiac sympathetic dysfunction, which is closely associated with diastolic dysfunction in HFpEF [36, 37]; Third, IR can impact HF by impairing cardiac metabolic flexibility and disrupting various energy metabolism

pathways [38]; Finally, IR leads to significant left ventricular dysfunction and promotes adverse myocardial remodeling, including increased left ventricular mass index and relative wall thickness [39]. Additionally, the substantial correlation between METS-IR and visceral fat levels also plays a critical role [11]. Visceral fat or abdominal obesity is not only associated with the incidence of HFpEF but also significantly linked to its poor prognosis [40, 41]. In a longitudinal, multicenter cohort study, VAT measured by CT was an effective predictor of HFpEF-related hospitalization even after multivariable adjustment; however, it did not predict HFrEF [42]. VAT can provide additional risk stratification for HFpEF even in individuals with overweight or obesity. Recent studies increasingly recognize cardiac adipose tissue within VAT as a critical factor in cardiovascular risk [43]. In HFpEF, epicardial adipose tissue may contribute to adverse clinical outcomes through several mechanisms, including lipid infiltration resulting in myocardial fatty degeneration, the promotion of local inflammation and fibrosis, as well as mechanical compression [44].

A key characteristic of HFpEF is its propensity to be associated with multiple extracardiac comorbidities. A large-scale multicenter heart failure cohort study from China demonstrated that HFpEF accounted for approximately 43.8% of the total heart failure population. Compared to other heart failure phenotypes, HFpEF was associated with a higher prevalence of comorbidities, including hypertension, stroke, pulmonary diseases, and atrial fibrillation [45]. We further conducted analyses across multiple subgroups based on different comorbidities and found that the predictive performance of METS-IR was consistently significant across all subgroups (all $P<0.05$). Additionally, we found that the predictive efficacy of METS-IR appeared to be more pronounced in individuals without hypertension or obesity. This may be due to the fact that individuals with hypertension or obesity are more likely to have other coexisting metabolic abnormalities or confounding factors, which could obscure or weaken the association between IR and outcomes. However, the specific mechanisms and underlying causes of this phenomenon require further investigation in future clinical and fundamental research. Furthermore, we performed an exploratory analysis to evaluate whether the predictive ability of METS-IR is influenced by the severity of comorbidities, as indicated by the ACCI scores. The results showed that the ability of METS-IR to predict all-cause mortality is relatively more pronounced at the highest ACCI scores, whereas its ability to predict CV death appears to be stronger at the lowest ACCI scores, although the interaction test has not yet reached statistical significance. This may be because, although IR can exacerbate both cardiac diseases and noncardiogenic comorbidities [46–48], in individuals with a greater comorbidity burden, noncardiogenic diseases may have a more pronounced impact on prognosis. Conversely, in individuals with fewer or less severe comorbidities, cardiogenic factors may play a greater role in determining prognosis. It is important to note that this part of the findings primarily serves as an exploratory extension of the overall study and may be influenced by random errors or other confounding factors, warranting cautious interpretation and requiring confirmation in larger-scale future studies. Nonetheless, it still suggests the potential need for more nuanced risk assessments and management strategies tailored to the varying comorbidity burdens in individuals with HFpEF to improve their prognosis. Finally, another major finding of this study was that adding METS-IR to the baseline predictive model significantly improved its efficacy in predicting mortality risk.

Strengths and limitations

Our study has several advantages. First, it was based on a multicenter cohort, thus enhancing its representativeness. Second, it was the first to explore the prognostic value of METS-IR in HFpEF, and it conducted exploratory analyses under various comorbid conditions. Additionally, we included a wide range of baseline characteristics in our multivariate analysis to minimize confounding from these factors and conducted propensity score matching analysis.

Several limitations that should also be noted. First, due to the retrospective nature of the study, comprehensive control over clinical data changes during the follow-up period was unattainable. Second, the absence of baseline insulin measurements prevented the calculation of HOMA-IR values and subsequent comparison with METS-IR. Third, the follow-up phase could be influenced by a degree of recall or reporting bias. Fourth, unmeasured confounding factors may affect the outcomes, requiring careful interpretation of the results. Ultimately, while our research indicated that METS-IR possessed prognostic relevance for HFpEF, its actual value in clinical practice still requires validation via future prospective studies.

Conclusions

METS-IR has significant predictive value for adverse outcomes in individuals with HFpEF. Furthermore, as a simple, readily available, and reliable surrogate marker of IR, it can effectively assist in the risk assessment and clinical management of HFpEF.

Abbreviations

HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
CVD	Cardiovascular disease

IR	Insulin resistance
HEC	Hyperinsulinemic-euglycemic clamp
METS-IR	Metabolic score for insulin resistance
IHD	Ischemic heart disease
HTN	Hypertension
VAT	Visceral adipose tissue
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
IQR	interquartile range
CV death	Cardiovascular death
BMI	Body mass index
MAP	Mean arterial pressure
HR	Heart rate
NYHA	New York Heart Association
AF	Atrial fibrillation
CKD	Chronic kidney disease
PAD	Peripheral arterial disease
WBC	White blood cell
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
TG	Triglyceride
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
NT-proBNP	N-terminal pro-brain natriuretic peptide
LVEF	Left ventricular ejection fraction
ACEI/ARB/ARNI	Angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitors
CCB	Calcium channel blockers
hospita inhibitors	Sodium-glucose co-transporter-2 inhibitors
MAGGIC score	Meta-analysis Global Group in Chronic Heart Failure score
ACCI	Age-adjusted Charlson comorbidity index
PSM	Propensity score matching
RCS	Restricted cubic spline
NRI	Net reclassification index
IDI	Integrated discrimination improvement
HR	Hazard ratio
CI	Confidence interval
SD	Standard deviation
ROC curve	Receiver operator characteristic curve
DCA	Decision curve analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01463-0.

Additional file 1: Fig. S1. HRs for all-cause death and CV death in HFpEF using spline analyses adjusted for Model 2.

Additional file 2: Fig. S2. Kaplan–Meier estimation of all-cause death across tertiles of METS-IR among different subgroups defined by comorbidities.

Additional file 3: Fig. S3. Kaplan–Meier estimation of CV death across tertiles of METS-IR among different subgroups defined by comorbidities.

Additional file 4: Fig. S4. Decision curve analysis comparing the baseline risk model with its integration of the METS-IR.

Additional file 5: Table S1. Univariable analysis of the relationship between each predictor and mortality. **Table S2**. Baseline characteristics of the study population according to METS-IR tertiles after PSM analysis. **Table S3**. HRs of primary outcomes according to METS-IR tertiles after PSM analysis. **Table S4**. HRs of primary outcomes according to METS-IR tertiles among different subgroups based on comorbidities. **Table S5**. HRs of primary outcomes according to METS-IR tertiles based on ACCI scores.

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Author contributions
All authors have made significant contributions. YZ performed the implementation of the study and manuscript preparation. YZ, YX and LD were responsible for performing the data collection and statistical analysis. YX and JD engaged in the discussion and revision of the manuscript. KH designed and supervised the experiments, serving as the corresponding author. All authors have read and approved the final manuscript for publication.

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Data availability
The datasets utilized and analyzed in this study are accessible from the corresponding author upon reasonable request.

Declarartions

Ethics approval and consent to participate
This study followed the principles of the Declaration of Helsinki and was approved by the ethics committees of The Affiliated Hospital of Henan University of Science and Technology and the PLA General Hospital. Due to the retrospective nature of this study, the institutional review board waived the requirement for informed consent, and all patient-identifying information was anonymized.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

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